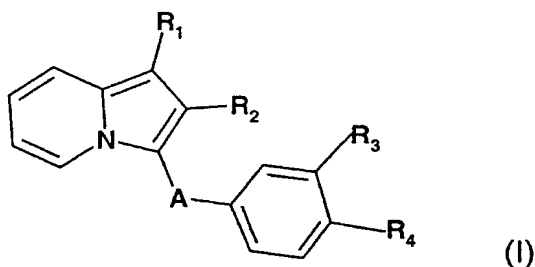


CLAIMS

1. Compounds of formula I,



5

in which

- R_1 represents a hydroxyl radical, a linear or branched alkoxy radical of 1 to 5 carbon atoms, a carboxyl radical, an alkoxycarbonyl radical of 2 to 6 carbon atoms or a radical of formula:

10

- $-NR_5R_6$
- $-NH-SO_2-Alk$
- $-NH-SO_2-Ph$
- $-NH-CO-Ph$
- $-N(Alk)-CO-Ph$
- $-NH-CO-NH-Ph$
- $-NH-CO-Alk$
- $-NH-CO_2-Alk$
- $-O-(CH_2)_n-cAlk$
- $-O-Alk-COOR_7$
- $-O-Alk-O-R_8$
- $-O-Alk-OH$
- $-O-Alk-C(NH_2):NOH$

15

20

- -O-Alk-NR₅R₆
- -O-Alk-CN
- -O-(CH₂)_n-Ph
- -O-Alk-CO-NR₅R₆
- 5 • -CO-NH-(CH₂)_m-COOR₇
- -CO-NH-Alk

in which

- 10 • Alk represents an alkyl radical or a linear or
branched alkylene radical of 1 to 5 carbon
atoms,
- cAlk represents a cycloalkyl radical of 3 to 6
carbon atoms,
- n represents an integer from 0 to 5,
- 15 • m represents an integer from 1 to 5,
- R₅ and R₆, which are identical or different,
each represent a hydrogen atom, a linear or
branched alkyl radical of 1 to 5 carbon atoms or
a benzyl radical,
- 20 • R₇ represents a hydrogen atom or an alkyl
radical of 1 to 5 carbon atoms,
- R₈ represents an alkyl radical of 1 to 5 carbon
atoms or a radical -CO-Alk,
- Ph represents a phenyl radical which is
- 25 optionally substituted with one or more halogen
atoms, with one or more alkoxy radicals of 1 to
5 carbon atoms, with one or more carboxyl

radicals or with one or more alkoxy carbonyl radicals of 2 to 6 carbon atoms,

- **R₂** represents a hydrogen atom, an alkyl radical of 1 to 5 carbon atoms, an alkyl halide radical of 1 to 5 carbon atoms containing 3 to 5 halogen atoms, a cycloalkyl radical of 3 to 6 carbon atoms or a phenyl radical which is optionally substituted with one or more halogen atoms, with one or more alkoxy radicals of 1 to 5 carbon atoms, with one or more carboxyl radicals or with one or more alkoxy carbonyl radicals of 2 to 6 carbon atoms,
- **A** represents a radical -CO-, -SO- or -SO₂-,
- **R₃** and **R₄**, which are identical or different, each represent a hydrogen atom, an alkoxy radical of 1 to 5 carbon atoms, an amino radical, a carboxyl radical, an alkoxy carbonyl radical of 2 to 6 carbon atoms, a hydroxyl radical, a nitro radical, a hydroxyamino radical, a radical of formula
 - -Alk-COOR₇
 - -NR₅R₆
 - -NH-Alk-COOR₇
 - -NH-COO-Alk
 - -N(R₁₁)-SO₂-Alk-NR₉R₁₀
 - -N(R₁₁)-SO₂-Alk
 - -N(R₁₁)-Alk-NR₅R₆
 - -N(R₁₁)-CO-Alk-NR₉R₁₀
 - -N(R₁₁)-CO-Alk

- -N(R₁₁)-CO-CF₃
- -NH-Alk-HetN
- -O-Alk-NR₉R₁₀
- -O-Alk-CO-NR₅R₆
- 5 • -O-Alk-HetN

in which n, m, Alk, R₅, R₆ and R₇ have the meaning given above for R₁, and

- R₉ and R₁₀, which are identical or different, each represent a hydrogen atom or an alkyl radical of 1 to 5 carbon atoms,
- 10 • R₁₁ represents a hydrogen atom or a radical -Alk-COOR₁₂ where R₁₂ represents a hydrogen atom, an alkyl radical of 1 to 5 carbon atoms or a benzyl radical,
- 15 • HetN represents a 5- or 6-membered heterocycle containing at least one nitrogen atom and optionally another heteroatom chosen from nitrogen and oxygen,
- or R₃ and R₄ form together a 5- to 6-membered unsaturated heterocycle, provided, however, that
- 20 when R₃ represents an alkoxy radical and R₄ represents a radical -O-Alk-NR₉R₁₀ or a hydroxyl radical, R₁ does not represent an alkoxy radical, optionally in the form of one of their
- 25 pharmaceutically acceptable salts.

2. Compounds of formula I, according to Claim 1, in which

- R_1 represents a hydroxyl radical, a linear or branched alkoxy radical of 1 to 5 carbon atoms, a carboxyl radical, an alkoxycarbonyl radical of 2 to 6 carbon atoms or a radical of formula:

- 5 • $-NR_5R_6$
- $-NH-SO_2-Alk$
- $-NH-SO_2-Ph$
- $-NH-CO-Ph$
- $-N(Alk)-CO-Ph$
- 10 • $-NH-CO-NH-Ph$
- $-NH-CO-Alk$
- $-NH-CO_2-Alk$
- $-O-(CH_2)_n-cAlk$
- $-O-Alk-COOR_7$
- 15 • $-O-Alk-O-R_8$
- $-O-Alk-OH$
- $-O-Alk-NR_5R_6$
- $-O-Alk-CN$
- $-O-(CH_2)_n-Ph$
- 20 • $-O-Alk-CO-NR_5R_6$
- $-CO-NH-(CH_2)_m-COOR_7$
- $-CO-NH-Alk$

in which

- Alk represents an alkyl radical or a linear or branched alkylene radical of 1 to 5 carbon atoms,

- cAlk represents a cycloalkyl radical of 3 to 6 carbon atoms,
- n represents an integer from 0 to 5,
- m represents an integer from 1 to 5,
- 5 • R₅ and R₆, which are identical or different, each represent a hydrogen atom, a linear or branched alkyl radical of 1 to 5 carbon atoms or a benzyl radical,
- R₇ represents a hydrogen atom or an alkyl radical of 1 to 5 carbon atoms,
- 10 • R₈ represents an alkyl radical of 1 to 5 carbon atoms or a radical -CO-Alk,
- Ph represents a phenyl radical which is optionally substituted with one or more halogen atoms, with one or more alkoxy radicals of 1 to 5 carbon atoms, with one or more carboxyl radicals or with one or more alkoxycarbonyl radicals of 2 to 6 carbon atoms,
- 15 - R₂ represents an alkyl radical of 1 to 5 carbon atoms, a trifluoromethyl radical, a cycloalkyl radical of 3 to 6 carbon atoms or a phenyl radical which is optionally substituted with one or more halogen atoms, with one or more alkoxy radicals of 1 to 5 carbon atoms, with one or more carboxyl radicals or with one or more alkoxycarbonyl radicals of 2 to 6 carbon atoms,
- 20 - A represents a radical -CO- or -SO₂-,
- 25

- R_3 and R_4 , which are identical or different each represent a hydrogen atom, an alkoxy radical of 1 to 5 carbon atoms, an amino radical, a carboxyl radical, an alkoxycarbonyl radical of 2 to 6 carbon atoms, a nitro radical, a hydroxyamino radical, a radical of formula
- $-\text{Alk}-\text{COOR}_7$
 - $-\text{NR}_5\text{R}_6$
 - $-\text{NH}-\text{Alk}-\text{COOR}_7$
 - $-\text{NH}-\text{COO}-\text{Alk}$
 - $-\text{N}(\text{R}_{11})-\text{SO}_2-\text{Alk}-\text{NR}_9\text{R}_{10}$
 - $-\text{N}(\text{R}_{11})-\text{SO}_2-\text{Alk}$
 - $-\text{N}(\text{R}_{11})-\text{Alk}-\text{NR}_5\text{R}_6$
 - $-\text{N}(\text{R}_{11})-\text{CO}-\text{Alk}-\text{NR}_9\text{R}_{10}$
 - $-\text{N}(\text{R}_{11})-\text{CO}-\text{Alk}$
 - $-\text{N}(\text{R}_{11})-\text{CO}-\text{CF}_3$
 - $-\text{NH}-\text{Alk}-\text{HetN}$
- in which n , m , Alk , R_5 , R_6 and R_7 have the meaning given above for R_1 , and
- R_9 and R_{10} , which are identical or different, each represent a hydrogen atom or an alkyl radical of 1 to 5 carbon atoms,
 - R_{11} represents a hydrogen atom or a radical $-\text{Alk}-\text{COOR}_{12}$ where R_{12} represents a hydrogen atom, an alkyl radical of 1 to 5 carbon atoms or a benzyl radical,

- HetN represents a 5- or 6-membered heterocycle containing at least one nitrogen atom and optionally another heteroatom chosen from nitrogen and oxygen,
5 optionally in the form of one of their pharmaceutically acceptable salts.

3. Compounds of formula I, according to either of Claims 1 and 2, in which

- **R₁** represents an alkoxy radical of 1 to 5 carbon
10 atoms, a carboxyl radical, a radical -O-Alk-COOH in which Alk represents an alkylene radical of 1 to 5 carbon atoms, a radical of formula -O-Alk-Ph in which Alk represents an alkylene radical of 1 to 5 carbon atoms and Ph represents a phenyl
15 radical which is optionally substituted with one or more halogen atoms or with one or more alkoxy radicals of 1 to 5 carbon atoms or with one or more carboxyl radicals, a radical of formula -NH-CO-Ph, a radical of formula -NH-SO₂-Ph or a
20 radical of formula -NH-CO-NH-Ph,
- **R₂** represents an alkyl radical of 1 to 5 carbon atoms,
- **A** represents a radical -CO-,
- **R₃** and **R₄**, which are different, each represent a
25 hydrogen atom, an alkoxy radical of 1 to 5 carbon atoms, an amino radical, a carboxyl radical or an alkoxycarbonyl radical of 2 to 6 carbon atoms,

optionally in the form of one of their pharmaceutically acceptable salts.

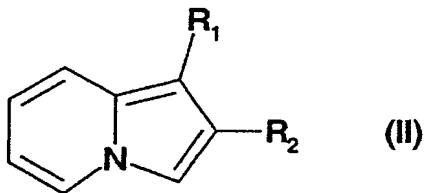
4. Compound of formula I, according to Claim 1, chosen from the following compounds:

- 5 - (4-amino-3-methoxyphenyl) (1-methoxy-2-methylindolizin-3-yl)methanone
- 3-(4-amino-3-methoxybenzoyl)-2-methylindolizin-1-yl carboxylic acid
- 2-([3-(4-amino-3-methoxybenzoyl)-2-methylindolizin-1-yl]oxy)acetic acid
- 10 - (4-amino-3-methoxyphenyl) {1-[(4-chlorobenzyl)oxy]-2-methylindolizin-3-yl}methanone
- (4-amino-3-methoxyphenyl) {1-[(3-methoxybenzyl)oxy]-2-methylindolizin-3-yl}methanone
- 15 - 4-([3-(4-amino-3-methoxybenzoyl)-2-methylindolizin-1-yl]oxy)methyl)benzoic acid
- 3-(4-carboxybenzoyl)-2-methylindolizin-1-yl carboxylic acid
- 20 - methyl 3-[(1-methoxy-2-methylindolizin-3-yl)carbonyl]benzoate
- 4-[(1-methoxy-2-methylindolizin-3-yl)carbonyl]benzoic acid
- 25 - 2-amino-5-[(1-methoxy-2-methylindolizin-3-yl)carbonyl]benzoic acid

- 2-amino-5-({1-[(3-methoxybenzoyl)amino]-2-methylindolizin-3-yl}carbonyl)benzoic acid
 - 2-amino-5-({2-methyl-1-[(3,4,5-trimethoxybenzoyl)amino]indolizin-3-yl}carbonyl)benzoic acid
 - 2-amino-5-({1-[(3-methoxyphenyl)sulphonyl]amino}-2-methylindolizin-3-yl}carbonyl)benzoic acid
- optionally in the form of one of its pharmaceutically acceptable salts.

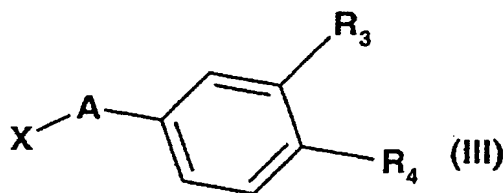
5. Method for preparing the compounds of formula I according to Claims 1 to 4, characterized in that

A) an indolizine derivative of formula II,

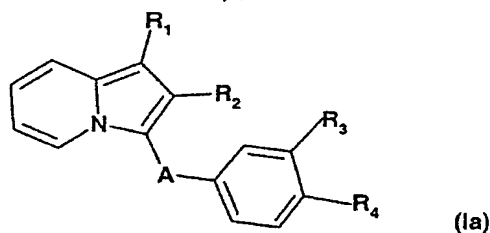


in which R_1 and R_2 have the meaning given for formula I, but R_2 does not represent a hydrogen atom or an alkyl halide radical,

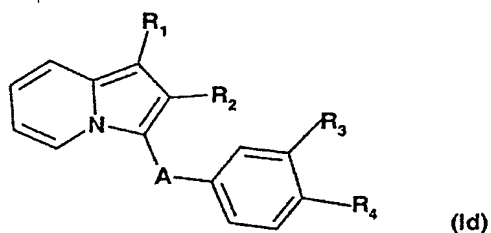
is condensed with a derivative of formula III,



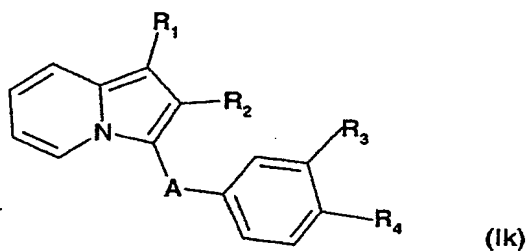
in which X represents a halogen atom and R_3 or R_4 , which are identical or different, each represent a hydrogen atom, a nitro radical, a trifluoroacetamido radical or an alkoxy carbonyl radical of 2 to 6 carbon atoms, in order to obtain the compounds of formula Ia, Id or Ik,



R_3 and/or $R_4 = \text{NO}_2$



R_3 and/or $R_4 = -\text{CO}_2\text{Alkyl}$



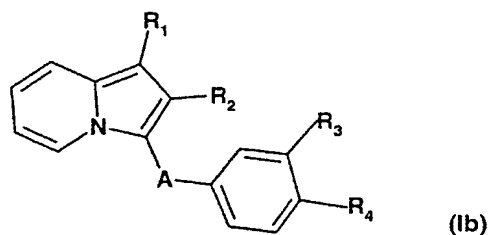
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R_3 and/or $R_4 = -\text{NH}-\text{COCF}_3$

and then,

- a) the compounds of formula Ia are subjected to a reduction in order to obtain the compounds of formula Ib,

15



R_3 and/or $R_4 = -NH_2$

in which R_3 and/or R_4 represent an amino radical, which compounds of formula Ib then

- are subjected to the action of an alkyl halide in order to obtain the compounds of formula I for which R_4 and/or R_3 represent a radical $-NR_5R_6$ (in which R_5 represents a hydrogen atom and R_6 represents an alkyl radical of 1 to 5 carbon atoms) and a radical $-NH-Alk-NR_5R_6$ or a radical $-NH-Alk-COOR_7$ (in which R_7 does not represent a hydrogen atom) from which, by a subsequent saponification, the compounds of formula I are obtained for which R_4 and/or R_3 represent a radical $-NH-Alk-COOR_7$ in which R_7 represents a hydrogen atom,

or

- are subjected to acylation in order to obtain the compounds of formula I for which R_4 and/or R_3 represent a radical $-NH-CO-Alk$, or a radical $-NH-CO-Alk-NR_9R_{10}$, which are then subjected to alkylation in

order to obtain a radical $-N(R_{11})-CO-Alk$ or
 a radical $-N(R_{11})-CO-Alk-NR_9R_{10}$ where R_{11}
 represents a radical $-Alk-COOR_{12}$ in which
 R_{12} does not represent a hydrogen atom, the
 5 latter compounds are then optionally
 subjected to saponification in order to
 obtain the compounds of formula I for which
 R_4 and/or R_3 represent a radical
 $-N(R_{11})-CO-Alk$ or a radical
 10 $-N(R_{11})-CO-Alk-NR_9R_{10}$ where R_{11} represents a
 radical $-Alk-COOH$,

or

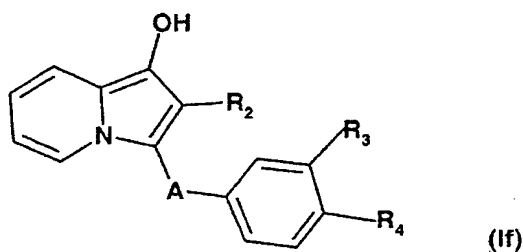
- are subjected to sulphonylation in order to
 obtain the compounds of formula I for which
 15 R_4 and/or R_3 represent a radical $-NH-SO_2-Alk$
 or a radical $-NH-SO_2-Alk-NR_9R_{10}$, which are
 then subjected to alkylation in order to
 obtain a radical $-N(R_{11})-SO_2-Alk$ or a
 radical $-N(R_{11})-SO_2-Alk-NR_9R_{10}$ where R_{11}
 20 represents a radical $-Alk-COOR_{12}$ in which
 R_{12} does not represent a hydrogen atom, the
 latter compounds are then optionally
 subjected to saponification in order to
 obtain the compounds of formula I for which
 25 R_4 and/or R_3 represent a radical
 $-N(R_{11})-SO_2-Alk$ or a radical

-N(R₁₁)-SO₂-Alk-NR₉R₁₀ where R₁₁ represents a radical -Alk-COOH

b) the compounds of formula Id in which R₃ and/or R₄ represent an alkoxy carbonyl radical are subjected to saponification in order to obtain the compounds of formula I in which R₃ and/or R₄ represent a carboxyl radical,

or

c) when R₁ represents a benzyloxy radical, the compounds of formula Ia are subjected to the action of trifluoroacetic acid or the compounds of formula Id to hydrogenation, in order to obtain the compounds of formula If,

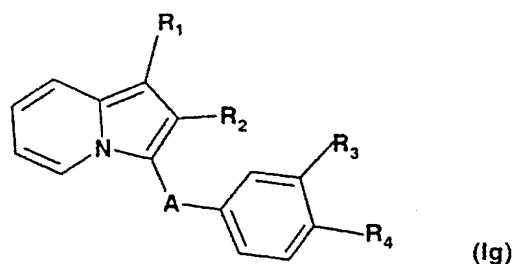


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in which R₃ and/or R₄ have the meanings given above,

and then the compounds of formula If are subjected to O-alkylation in order to obtain the compounds of formula Ig,

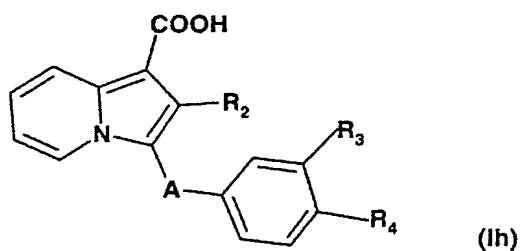
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in which R_3 and/or R_4 have the meanings given above, and R_1 represents a linear or branched alkoxy radical of 1 to 5 carbon atoms, a radical $-O-(CH_2)_n-cAlk$, a radical $-O-Alk-COOR_7$, a radical $-O-Alk-NR_5R_6$, a radical $-O-(CH_2)_n-Ph$, or a radical $-O-Alk-O-R_8$ - which, when R_8 represents a radical $-COCH_3$, can give, by subsequent saponification, a radical $-O-Alk-OH$ - or a radical $-O-Alk-CN$ which, by treatment with hydroxylamine, gives a radical $-O-Alk-C(NH_2)=NOH$,

or

d) when R_1 represents an alkoxycarbonyl radical, the compounds of formula Ia are subjected to saponification in order to obtain the compounds of formula Ih,



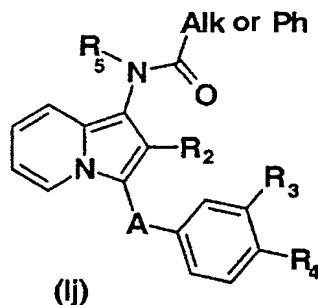
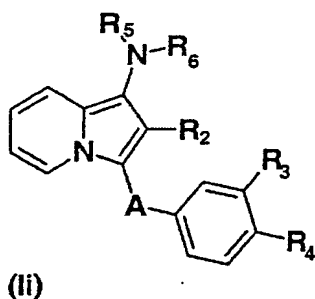
in which R_3 and/or R_4 have the meanings given above, which are then subjected to the action of an amine derivative in order to obtain the compounds of formula I in which R_1 represents a radical $-\text{CO}-\text{NH}-\text{Alk}$, or to the action of an amino acid derivative in order to obtain the compounds of formula I in which R_1 represents a radical $-\text{CO}-\text{NH}-(\text{CH}_2)_m-\text{COOR}_7$

or

e) when R_1 represents a radical $-\text{NH}-\text{CO}_2\text{tButyl}$, the compounds of formula Ia or Id are subjected

- either to alkylation followed by deprotection and an optional second alkylation in order to obtain the compounds of formula Ii,

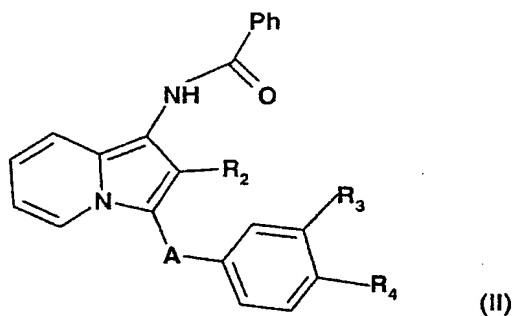
- or to deprotection, followed by acylation in order to obtain the compounds of formula Ij in which R_5 represents a hydrogen atom, followed by an optional alkylation in order to obtain the compounds of formula Ij in which R_5 represents an alkyl radical



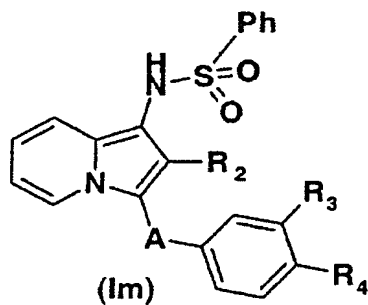
or

f) when R_1 represents a radical $-NH-CO_2tButyl$, the compounds of formula **Ik** are subjected

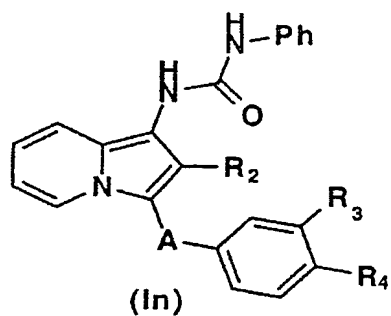
• either to deprotection, followed by acylation in order to obtain the compounds of formula **II**



• or to deprotection followed by sulphonylation in order to obtain the compounds of formula **Im**

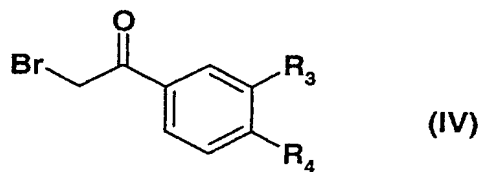


• or to deprotection, followed by a treatment with a phenyl isocyanate in order to obtain the compounds of formula **In**



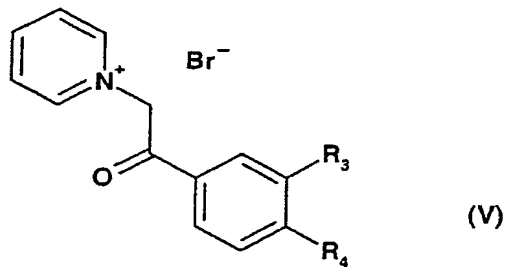
OR

- 5 **B)** when R_1 represents an electron-attracting group, R_2 represents a hydrogen atom or an alkyl halide radical and A represents a radical $-CO-$, pyridine is reacted with a bromoacetophenone of formula IV,



10

in order to obtain the compounds of formula V,



15

which are then subjected to a 1,3-dipolar cycloaddition with ethyl acrylate or a halogenated derivative of

ethyl crotonate in the presence of an oxidizing agent in order to obtain the compounds of formula Ia in which R_1 represents an ethoxycarbonyl radical and R_2 represents a hydrogen atom or an alkyl halide radical.

5 6. Pharmaceutical composition containing, as active ingredient, a compound of formula I, according to any one of Claims 1 to 4, optionally in combination with one or more inert and appropriate excipients.

10 7. Pharmaceutical composition according to Claim 6, which is useful in the treatment of diseases requiring modulation of b-FGFs.

 8. Pharmaceutical composition according to Claim 6, which is useful in the treatment of carcinomas
15 having a high degree of vascularization, such as carcinomas of the lung, breast, prostate and oesophagus, cancers which induce metastases, such as colon cancer and stomach cancer, melanomas, gliomas, lymphomas and leukaemias.

20 9. Pharmaceutical composition according to Claim 6, which is useful in the treatment of cardiovascular diseases such as atherosclerosis, post-angioplasty restinosis, diseases linked to complications which appear following the fitting of
25 endovascular prostheses and/or aorto-coronary artery by-pass surgery or other vascular transplants, cardiac

hypertrophy, or vascular complications in diabetes such as diabetic retinopathies.

10. Pharmaceutical composition according to Claim 6, which is useful in the treatment of chronic
5 inflammatory diseases such as rheumatoid arthritis or IBDs.

11. Pharmaceutical composition according to Claim 6, which is useful in the treatment of achondroplasia (ACH), hypochondroplasia (HCH) and TD
10 (thanatophoric dysplasia).

12. Use of a compound of formula I according to Claim 1, for the preparation of a pharmaceutical composition which is useful in the treatment of diseases requiring modulation of b-FGFs.